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EXAMINER
ZARA, JANE J

ART UNIT	PAPER NUMBER
1635	28

DATE MAILED: 09/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary

Application No.	Applicant(s)
09/243,102	MacLachlan et al
Examiner	**Art Unit**
Jane Zara	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jun 30, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-12, 14-35, 37-41, and 43-61* is/are pending in the application.

4a) Of the above, claim(s) *29-34* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-12, 14-28, 35, 37-41, and 43-61* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This Office action is in response to the communications filed April 8, 2003 and June 30, 2003, Paper Nos. 24 and 25, respectively.

Claims 1-12, 14-35, 37-41 and 43-61 are pending in the instant application.

The declaration under 37 CFR 1.132 filed June 30, 2003 is sufficient to overcome the rejection of claims 1-28 and 35-46 based upon 35 U.S.C. 112, first paragraph.

Response to Arguments and Amendments

Any rejections not repeated in this Office action are hereby withdrawn.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12, 14-35, 37-41, 43-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1, 47 and 48, the metes and bounds of treating a tumor, as recited in claim 1, and in relation to the recitation of the limitation in claim 47, lines 6-7, wherein the tumor is reponsive to a gene product, and in relation to the recitation of the limitation in claim 48, lines 6-7, wherein

the cells of a tumor are transfectable, are unclear (e.g what is encompassed by treating a tumor in claim 1, and how can a non-treatable tumor, or a non-tranfectable tumor cell be determined?

In claim 2, line 2, "said nucleic acid" lacks antecedent basis.

In claim 2, line 2, the term "an expressible gene" is vague and unclear. Appropriate clarification is requested.

In claim 4, line 2, it is unclear what the term "heterologous" refers to (e.g. heterologous to a gene in the organism being treated?). Appropriate clarification is requested.

In claim 7, line 2, it is unclear what the term "homologous" refers to (e.g. homologous to a gene in the organism being treated?). Appropriate clarification is requested.

In claim 10, line 2, it is unclear what is encompassed by "a therapeutically effective amount of said gene is generated at said tumor" (e.g. Is this the result of replication, transcription, translation of a polypeptide?). Appropriate clarification is requested.

In claim 15, lines 3-4, the phrase "at a rate faster than PEG-Cer20" is vague and unclear (e.g. perhaps inserting --that of-- before "PEG-Cer20" would be remedial).

Claim 22 recites the limitation "said nucleic acid-lipid particles" in line 2. There is insufficient antecedent basis for this limitation in the claim (e.g. Since "particles" is plural, changing "said" to --the-- would be remedial).

In claim 26, it is unclear whether the limitation described in lines 2-3, of the nucleic acid remaining at least 90% intact upon treatment with DNAse, is further limiting from claim 1. Also

in claim 26, it is unclear how this characteristic would be determined in vivo (perhaps inserting the stipulation --in vitro-- after "treated" in line 3 would be remedial).

Claim 28 recites the limitation "said administering" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claims 37 and 38 depend from claim 36, which has been canceled.

Claim 59 recites the limitation "the tumor suppressor protein". There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12, 14-35, 37-41, 43-61 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a tumor that is responsive to a nucleic acid comprising the administration of the nucleic acid into the tumor cell, does not reasonably provide enablement for a method of treating a tumor that is non-responsive to a nucleic acid comprising the administration of the nucleic acid into the tumor cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to methods of treating a treatable and non-treatable tumor, as well as treating a tumor comprising transfectable and non-transfectable cells in a mammal, which methods comprise the adminstration of a nucleic acid encapsulated in a lipid-nucleic acid particle. The specification and claims lack the guidance to determine a tumor cell that is non-responsive to a gene product from a responsive tumor cell. The specification and claims lack sufficient guidance for the determination of a transfectable from a non-transfectable tumor cell in an animal. It would require undue experimentation beyond that which has been provided in the instant disclosure to determine a non-responsive or non-transfectable tumor cell from a responsive or transfectable tumor cell in an organism. Furthermore, transfection is a method that refers to the transfer of nucleic acids into a target cell in vitro, and relationship between transfectable cell in vitro and treatable tumor cell in vivo is not necessarily clear. Therefore, the instant invention is not enabled for the scope drawn to the treatment of tumor cells in a mammal, which treatment comprises the administration of lipid-encapsulated nucleic acids to non-responsive and responsive tumor cells, as well as to non-transfectable and transfectable tumor cells in an organism.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who

has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-5, 7, 8, 10-12, 14-26, 28, 43-49 and 53 are rejected under 35 U.S.C. 102(e) as being by anticipated by Semple et al.

Semple et al teach methods of treating a tumor in a mammal comprising the distal administration, including intravenous administration, at least once in eight weeks, of a serum stable (nuclease resistant) nucleic acid-lipid particle comprising a fully encapsulated nucleic acid comprising an expressible gene that is either homologous or heterologous to a gene in the mammal, which nucleic acid encodes a therapeutic polynucleotide (a ribozyme), or encodes a therapeutic polypeptide (cytokine), which therapeutic molecule is expressed and accumulates in a therapeutically effective amount at the site of the tumor (i.e. >0.5% of dose administered), which particle comprises DODAC, DOPE, cholesterol and a PEG-lipid, which particles are uniform in size and between 60-130 nm, with a nucleic acid: lipid ratio greater than 25mg nucleic acid:mmole lipid (See entire document, especially the abstract; col. 4-6; col. 8-9; col. 12-14; col. 20; example 4, col. 28-36; claims 1-72).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 5, 6, 9, 27, 35, 37-41, 47 and 50-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Semple et al in view of the combined teachings of Fulton et al, Hung et al, Zhuang et al and Chaudhary et al.

The claims are drawn to methods of treating a tumor in a mammal comprising the distal administration of a serum stable (nuclease resistant) nucleic acid-lipid particle comprising a fully encapsulated nucleic acid comprising an expressible gene encoding HSVTK (a suicide enzyme) or IL-12 (a cytokine), and optionally further comprising administration of a chemotherapeutic agent either before or after administration of the nucleic acid-lipid particle, or wherein the expressible

gene encodes a suicide enzyme and which method optionally further comprises administration of a prodrug before or after administration of the nucleic acid-lipid particle(s), or wherein the expressible gene encodes apoptin (a tumor suppressor protein) or Pseudomonas exotoxin, and

which particles comprise a cationic lipid, neutral lipid and lipid conjugate that prevents aggregation during formulation, and which tumor is a colorectal, sarcoma or melanoma tumor.

Semple et al teach methods of treating a tumor, including a melanoma tumor, in a mammal comprising the distal administration (intravenous administration) of a serum stable (nuclease resistant) nucleic acid-lipid particle comprising a fully encapsulated nucleic acid encoding a cytokine, which particles comprise a cationic lipid, neutral lipid and lipid conjugate that prevents aggregation during formulation (See entire document, especially the abstract; col. 4-6; col. 8-9; col. 12-14; col. 20; example 4, col. 28-36; claims 1-72).

Semple et al do not teach the administration of an expressible gene encoding HSVTK (a suicide enzyme) or IL-12, and optionally further comprising administration of a chemotherapeutic agent either before or after administration of the nucleic acid-lipid particle, or an expressible gene encoding a suicide enzyme and which method optionally further comprises administration of a prodrug before or after administration of the nucleic acid-lipid particle(s), or an expressible gene encoding apoptin (a tumor suppressor protein) or Pseudomonas exotoxin, nor the treatment of sarcoma or colorectal tumors.

Fulton et al teach methods of treating melanoma, sarcoma and colorectal tumors comprising the administration of nucleic acids encoding a tumor suppressor protein, interleukin 12 (IL-12) or thymidine kinase (HSVTK), optionally in combination with a prodrug administered either before or after administration of lipids and nucleic acids encoding either the tumor suppressor protein, IL-12 or HSVTK (See entire document, especially the abstract; col. 2; col. 10, line 53-col. 11, line 7; col. 33; col. 52-53; col. 56-58; col. 60; col. 62-63).

Hung et al teach the administration of nucleic acid-lipid particles or complexes to tumors, optionally including encapsulated nucleic acids in lipid particles, which nucleic acids encode therapeutic polynucleotides (ribozymes) or polypeptides, and optionally further comprising the administration of a chemotherapeutic agent either before or after administration of the nucleic acid-lipids (See especially col. 25-26; examples VI and VII, col. 45-50).

Zhuang et al teach the administration of apoptin to sarcoma cells to induce apoptosis (See especially the abstract and figure 4 on page 488).

Chaudhary et al teach the lysis of target cells by Pseudomonas exotoxin (See especially the abstract, figure 3 and table 1 on page 396).

It would have been obvious to one of ordinary skill in the art to treat sarcoma, melanoma or colorectal tumors with nucleic acids encapsulated in lipid particles, which nucleic acids encode a tumor suppressor protein, IL-12, HSVTK, apoptin or Pseudomonas exotoxin because these therapeutic molecules have been used previously by Semple, Fulton, Hung Zhuang and Chaudhary to treat tumors and one of ordinary skill in the art would have expected that the encapsulated

nucleic acids are delivered to the target tumor site following distal administration in therapeutically effective concentrations, inhibiting tumor cell growth and/or viability, thereby providing tumor treatment. One of ordinary skill in the art would have been motivated to administer the therapeutic, encapsulated nucleic acids to tumor cells optionally in combination with chemotherapeutic agents or prodrugs because Fulton and Hung have taught the enhanced treatment of target tumor cells using these combined therapies, and one of ordinary skill in the art would have expected that enhanced tumor cell kill or tumor treatment is obtained following administration of the nucleic acid-lipid particles as taught previously by Semple et al, either preceding or following prodrug or chemotherapeutic agent administration. One of ordinary skill in the art would have been motivated to encapsulate these therapeutic nucleic acids in lipid particles because Semple taught previously that enhanced protection of the nucleic acids from nuclease degradation is obtained upon lipid encapsulation of the nucleic acids. And one of ordinary skill in the art would have expected that enhanced tumor treatment is obtained using encapsulated nucleic acids because Semple has shown that encapsulation leads to enhanced nucleic acid stability, which in turn leads to enhanced nucleic acid delivery to the tumor sites, thereby providing delivery of appropriate therapeutic concentrations of the nucleic acids at the tumor site. Therefore, the claimed invention would have been obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ

September 8, 2003

RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER